

89. (New) The composition of claim 1 wherein said emulsion is an oil-in-water-in-oil emulsion or a water-in-oil-in-water emulsion.

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90. (New) The composition according to claim 1, wherein said oligonucleotide is selected from the group consisting of SEQ ID NOS: 2, 48, 56, 49, 57, 58, 50, 16, 19, 51, 52, 53, and 54.

91. (new) The composition according to claim 46, wherein said oligonucleotide is selected from the group consisting of SEQ ID NOS; 2, 48, 56, 49, 57, 58, 50, 16, 19, 51, 52, 53, and 54.

REMARKS

Claims 1-7, 10, 12-13, 15, 17, 19, 20, 46, 48-63, 80, 83 and 89-91 are pending. Claim 1 has been amended, support for which may be found throughout the specification as originally filed, for example, on pages 16-17 and in claim 18. Claims 80 and 83 have been amended to form four dependent claims. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the claims by the present amendment. The attached page is captioned "Version with markings to show changes made."

Claim of Priority

The Office Action suggests that the above referenced application is not entitled to benefit of the claim of priority to parent applications 09/108,673 and 08/886,829 for failure to find support for the present claims. Applicants do not concur.

The Office Action incorrectly denies Applicants' claim of priority on the basis that the parent application discloses that the compositions are useful for "alimentary delivery" and not "non-parenteral administration". With all due respect, this is not the correct standard for determining whether a **claimed** invention is entitled to claim the benefit of an earlier filed application. The claimed invention, which is directed to compositions, finds support in the 829 priority application as originally filed as provided, for example, in the table set forth below. Therefore, the invention as claimed is entitled to the earlier filing date of application 08/886,829, filed July 1, 1997.

CLAIM NO.	CLAIM LANGUAGE	SUPPORT IN 829 PRIORITY APPLICATION
1	A composition comprising at least one oligonucleotide in an emulsion and at least one penetration enhancer selected from the group consisting of surfactants, fatty acids, bile salts, chelating agents, non-chelating non-surfactant molecules, and combinations thereof; wherein said non-chelating non-surfactant is selected from the group consisting of unsaturated cyclic ureas, 1-alkyl-alkanones, 1-alkenylazacyclo-alkanones, non-steroidal anti-inflammatory agent, and combinations thereof.	Pages 10-13 & 30 Originally filed Claims 1, 2, & 14
2	The composition of claim 1 wherein said oligonucleotide is an antisense oligonucleotide.	Page 3 & Originally filed Claim 23
3	The composition of claim 1 wherein said oligonucleotide modulates expression of a cellular adhesion protein,	Pages 36, 46 & Originally filed claim 24

	modulates a rate of cellular proliferation, or has biological activity against eukaryotic pathogens or retroviruses.	
4	The composition claim 1 wherein said oligonucleotide is a ribozyme or a peptide nucleic acid.	Pages 20, 35 & 36
5	The composition of claim 1 wherein said emulsion is selected from the group consisting of an oil-in-water emulsion, a water-in-oil emulsion.	Page 31
6	The composition of claim 1 wherein said emulsion is a microemulsion.	Pages 63 & 64
10	The composition of claim 1 wherein said fatty acid is selected from a group consisting of arachidonic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprinate, tricaprinate, monoolein, dilaurin, glyceryl 1-monocaprinate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, a monoglyceride, a diglyceride and a pharmaceutically acceptable salt thereof.	Page 11 & Originally filed claim 5
12	The composition of claim 1 wherein said bile salt is selected from the group consisting of cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydrofusidate, sodium glycodihydrofusidate, polyoxyethylene-9-lauryl ether and a pharmaceutically acceptable salt thereof.	Pages 11, 12 & Originally filed claim 7
13	The composition of claim 1 wherein said penetration enhancer is a combination of at least one fatty acid and at least one bile salt.	Originally filed Claim 14
15	The composition of claim 1 wherein said chelating agent is selected from the group consisting of EDTA, citric acid, a salicylate, an <i>N</i> -acyl derivative of collagen, laureth-9, an <i>N</i> -amino acyl derivative of a beta-diketone and a mixture thereof.	Page 12 & Originally filed claim 9
17	The composition of claim 1 wherein said surfactant is selected from the group consisting of sodium lauryl sulfate, polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether, a perfluorchemical emulsion and a mixture thereof.	Pages 10, 11 & Originally filed claim 10
19	The composition of claim 1 further comprising at least one	Pages 13, 14, &

	carrier compound.	Originally filed Claim 12
20	The composition of claim 19 wherein said carrier compound is selected from the group consisting of polyinosinic acid, dextran sulfate, polycytidic acid, and 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid.	Page 13 & Originally filed Claim 13
46	A composition comprising an oligonucleotide in oral dosage form, wherein said oligonucleotide comprises at least one modified covalent linkage.	Pages 9-10, 19-20, & 29
48	The composition of claim 46 wherein said modified covalent linkage is selected from the group consisting of a phosphorothioate linkage, a phosphotriester linkage, a methyl phosphonate linkage, a methylene(methylimino) linkage, a morpholino linkage, an amide linkage, a polyamide linkage, a short chain alkyl intersugar linkage, a cycloalkyl intersugar linkage, a short chain heteroatomic intersugar linkage and a heterocyclic intersugar linkage.	Pages 19-20
49	The composition of claim 46 wherein at least one of the nucleotides of said oligonucleotide has a modified sugar moiety.	Pages 20-21
50	The composition of claim 49 wherein said modified sugar moiety has a substitution or addition at the 2' position of a moiety selected from the group consisting of -OH, -SH, -SCH ₃ , -F, -OCN, -OCH ₃ OCH ₃ , -OCH ₃ O(CH ₂) _n CH ₃ , -O(CH ₂) _n NH ₂ or -O(CH ₂) _n CH ₃ where n is from 1 to about 10, a C ₁ to C ₁₀ lower alkyl group, an alkoxyalkoxy group, a substituted lower alkyl group, a substituted alkaryl group, a substituted aralkyl group, -Cl, -Br, -CN, -CF ₃ , -OCF ₃ , an -O-alkyl group, an -S-alkyl group, an N-alkyl group, an O-alkenyl group, an S-alkenyl group, an N-alkenyl group, -SOCH ₃ , -SO ₂ CH ₃ , -ONO ₂ , -NO ₂ , -N ₃ , -NH ₂ , a heterocycloalkyl group, a heterocycloalkaryl group, an aminoalkylamino group, a polyalkylamino group, a substituted silyl group, an RNA cleaving group, a reporter group, a DNA intercalating group, a group for improving the pharmacokinetic properties of an oligonucleotide, a group for improving the pharmacodynamic properties of an oligonucleotide, a methoxyethoxy group and a methoxy group.	Page 21
51	The composition of claim 46 wherein said oligonucleotide comprises at least one modified nucleobase.	Page 20

52	The composition of claim 46 wherein said oral dosage form is selected from the group consisting of tablets, and capsules.	Page 29
53	The composition of claim 46 wherein said oligonucleotide is an antisense oligonucleotide.	Page 3
54	The composition of claim 46 wherein said oligonucleotide modulates expression of a cellular adhesion protein, modulates a rate of cellular proliferation, or has biological activity against eukaryotic pathogens or retroviruses.	Pages 36 & 46
55	The composition of claim 46 wherein said nucleic acid is a ribozyme or a peptide nucleic acid.	Pages 20, 35 & 36
56	The composition of claim 46 further comprising an enteric material that substantially prevents dissolution of said tablets, or capsules in a mammalian stomach.	Pages 29 & 30
57	The composition of claim 56 wherein said enteric material is a coating.	Page 30
58	The composition of claim 57 wherein said enteric coating is selected from the group consisting of acetate phthalate, propylene glycol, and sorbitan monoleate.	Page 30
59	The composition of claim 46 further comprising a penetration enhancer.	Pages 10-13
60	The composition of claim 59 wherein said penetration enhancer is selected from the group consisting of bile salts and fatty acids.	Pages 11-12
61	The composition of claim 60 wherein said bile salt is selected from the group consisting of ursodeoxycholic acid, chenodeoxycholic acid, and salts thereof.	Page 12
62	The composition of claim 60 wherein said fatty acids are selected from capric acid, lauric acid, and salts thereof.	Page 11
63	The composition of claim 46 further comprising an excipient.	Pages 30 & 31
80	The composition according to claim 1, wherein said oligonucleotide is SEQ ID NO: 1 or SEQ ID NO: 55.	Page 24
83	The composition according to claim 46, wherein said oligonucleotide is SEQ ID NO: 1 or SEQ ID NO: 55.	Page 24

Rejection under 35 U.S.C. §102(b)

Claims 1-7 and 10 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,591,840 to Narayanan *et al.* ("the Narayanan patent").

Applicants do not concur. However, for purposes of facilitating prosecution, Applicants have amended the claims to recite "non-chelating non-surfactant is selected from the group consisting of unsaturated cyclic ureas, 1-alkyl-alkanones, 1-alkenylazacyclo-alkanones, non-steroidal anti-inflammatory agent, and combinations thereof." In as much as the Narayanan reference does not disclose *any* of the penetration enhancers in claim 1, as amended. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 102(e)

Claims 1-7, 19-20, 46-64, 80 and 83 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,111,094A1 to Bennett *et al.* (hereinafter "the Bennett patent"). As discussed above, Applicants are entitled to their claim of priority to parent application serial no. 08/886,829, and, therefore to an effective filing date of July 1, 1997. The disclosure in the Bennett patent that serves as the basis for the rejection is not disclosed in its immediate parent (U.S. Patent No. 5,843,738). Thus, the subject matter over which the present inventions stand rejected has an effective filing date of April 17, 1998, the date on which the Bennett patent was filed. Accordingly, the Bennett patent does not constitute a proper § 102(e) reference. Applicants therefore respectfully request withdrawal of the rejection.

Claims 46 and 65-66 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,120,803A to Wong et al. (hereinafter "the Wong patent"). In view of Applicants' claim of priority, the present application is entitled to an effective filing date of July 1, 1997. Accordingly, the Wong patent, which was filed on August 10, 1998, does not qualify as prior art under 35 U.S.C. § 102(e), and cannot provide the basis for a rejection.

Applicants therefore respectfully request withdrawal of the rejection.

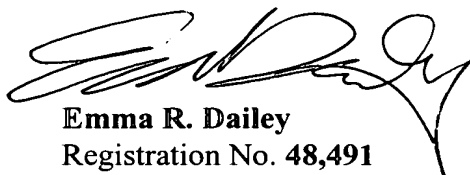
Claims 1-7, 9-20 and 46-62 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,877,309-A to McKay et al. (hereinafter "the McKay patent"). In view of Applicants' claim of priority, the present application is entitled to an effective filing date of July 1, 1997. Accordingly, the McKay patent, which was filed on August 13, 1997, does not qualify as prior art under 35 U.S.C. § 102(e), and cannot provide the basis for a rejection. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

DOCKET NO.: ISIS-3510

PATENT

Applicants respectfully submit that the claims presently before the Examiner patentably define the invention over the prior art and are otherwise in condition for ready allowance.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES**In the Claims**

Please cancel claims 18 and 64, without prejudice, and add claims 89-91. Please amend claims 1, 5, 80 and 83 as follows:

1. (Amended) A composition comprising at least one oligonucleotide in an emulsion and at least one penetration enhancer selected from the group consisting of surfactants, fatty acids, bile salts, chelating agents, non-chelating non-surfactant molecules, and combinations thereof;

wherein said non-chelating non-surfactant is selected from the group consisting of unsaturated cyclic ureas, 1-alkyl-alkanones, 1-alkenylazacyclo-alkanones, non-steroidal anti-inflammatory agents, and combinations thereof.

5. (Amended) The composition of claim 1 wherein said emulsion is [selected from the group consisting of] an oil-in-water emulsion [,] or a water-in-oil emulsion [, an oil-in-water-in-oil emulsion and a water-in-oil-in-water emulsion].

80. (amended) The composition according to claim 1, wherein said oligonucleotide is [selected from the group consisting of SEQ ID NOS: 1, 55, 2, 48, 56, 49, 57, 58, 50, 16, 19, 51, 52, 53, and 54] SEQ ID NO: 1 or SEQ ID NO: 55.

83. (amended) The composition according to claim 46, wherein said oligonucleotide is [selected from the group consisting of SEQ ID NOS: 1, 55, 2, 48, 56, 49, 57, 58, 50, 16, 19, 51, 52, 53, and 54] SEQ ID NO: 1 or SEQ ID NO: 55.